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ABSTRACT

A battery of behavioral tests yielding 79 measures, many of which were presumably related to learning and memory, was administered to house mice of seven inbred strains. An analysis of the factorial structure indicated that the two principal and most pervasive factors underlying performance on the battery involved the initiation and maintenance of locomotor activity. Thus, many of the genetically assisted behavioral differences between strains which have heretofore been considered to involve differences in learning and memory actually represent genetically associated differences in facets of activity. Chemical analyses of the brains of mice of the seven strains revealed substantial relations between the enzymes choline acetylase and monoamine oxidase and the activity maintenance factor. Among the amino acids, taurine and gamma-aminobutyric acid were shown to have substantial relations with the activity initiation factor. Thus, there do indeed appear to be some likely functional relations between some classes of behavior and specific neurotransmitter systems within the brain. (Author)

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Final Report

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INDIVIDUAL DIFFERENCES IN LEARNING AND MEMORY

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INTRODUCTION

The broad goal of the research project just completed was to establish relations between brain chemistry and behavior, particularly behavior related to learning. The primary hypotheses we made when we began our project were, in general, that different classes of behavior are associated with different functional neural systems which may be defined either anatomically or biochemically; and, specifically, that different chemical systems potentially related to transmitter activity are differentially involved in different classes of behavior. That is, were one to analyze behaviors into largely independent categories within each of which the behaviors were highly related (a taxonomy of behavior), a strong relation could be shown to exist between specific chemical systems and specific categories of behavior. Thus, variations within a specific chemically mediated neural subsystem might be associated with marked behavioral variations within one behavioral class, while behaviors in other classes might be substantially unaffected. One needs marked variability between organisms on a large variety of behaviors and in two or more neurochemical systems to explore the possibility of functional relations between brain chemistry and behavior, for one needs (a) to establish first a crude taxonomy of behavior, and (b) to have variation both for those taxonomic categories and for brain chemistry. For reasons developed in detail in the METHODS section, we chose to work with genetically associated variability in chemistry and behavior existing between inbred strains of house mice.

The specific objectives of the research project were to establish the existence of some reliable differences in behavioral characteristics between inbred strains of mice, and to investigate possible underlying genetically associated biochemical variations. We hoped to identify genetically determined patterns of behavior and of neurochemical activity and to use these genetically associated differences to assess the degree of involvement of different chemical systems in various behaviors. To achieve these aims, we selected seven genetically unrelated inbred strains of mice, administered a large battery of behavioral tests, and, in collaboration with others, carried out assays for the level of activity of five enzymes and 26 amino acids. The data were first analyzed for strain differences in behavior, and those measures for which a significant strain difference was obtained were employed in a series of factor analytic studies. It was hoped that the factor analyses would permit postulation of a small number of independent factors to account for inter-strain variability in behavior and help define the psychological nature of the individual tests, while the factor patterning of the neurochemical variables would permit identification of possible relations between chemistry and behavior.

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METHODS

Subjects

Inbred strains of mice are ideal subjects for the study of individual differences, for all members of a given strain are genetically identical, providing a characteristic of great experimental value: reproducibility. Insofar as their characteristics are genetic in origin, one member of a strain is like another. Experimentally, this means that they are ideal for correlational studies in which it is not possible to take multiple measurements on a single animal. Instead, one takes different measurements on different animals within an inbred strain and then proceeds inferentially as though they had, in fact, been taken on a single animal. In order to obtain a wide range of individual differences, a number of genetically unrelated strains of mice should be used. We selected seven strains available from The Jackson Laboratory, Bar Harbor, Maine, on the basis of their relative genetic independence, their availability, their lack of biological characteristics that would be an obvious detriment to learning (e.g. retinal degeneration), and what was already known about differences in their behavior. The origins of the seven strains and some of their characteristics are given below; the information is taken from the Handbook on Genetically Standardized JAX Mice, published by The Jackson Laboratory. All of the mice used in the study were males approximately 6 weeks to 6 months of age.

C57BL/6J: A subline of C57BL, which was originated by C. C. Little in 1921 from Lathrop's stock. Subline 6 established about 1937. This is a sturdy strain of black mice widely used as the standard strain for comparisons in many fields of research. This strain has average brain weight, high activity, learns one-way avoidance and visual discrimination tasks well, and is poor at two-way avoidance. Retention is not facilitated by post-trial etherization. These mice learn some tasks better under distributed than under massed practice conditions. They have a high preference for alcohol. They exhibit low audiogenic seizure susceptibility.

C57BR/cdJ: Origin: Little, 1921, from a mating that resulted in C57BL and C57BR. Subline cd was established in generation 13. This is a brown strain which has not been studied extensively behaviorally. This strain is similar in many respects to C57BL/6J, but is more active, more aggressive, and it has smaller brain.

DBA/2J: Origin: Little, 1909. Subline 2 was established 1929. A gray strain often used for comparison with C57BL/6J, from which it differs in a number of characteristics. This strain has a very low brain weight, exhibits medium activity, learns one-way avoidance and visual discrimination tasks well, and is average on two-way avoidance. Mice of this strain learn some tasks better under massed than distributed conditions of practice. Memory can be facilitated by post-learning treatment with ether. Mice of this strain have a low preference for alcohol. Mice of this strain possess a very high susceptibility to audiogenic seizures at 4-5 weeks of age.

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CBA/CaJ: Origin: Strong, 1920, from a cross between Bagg albino and DBA. A subline of strain CBA, but unlike the parent strain, CBA/CaJ does not have retinal degeneration (rd). Very few studies have been carried out on this subline of the agouti strain CBA/J. The latter line has high brain weight, and is low on activity and aggressiveness.

CE/J: Origin: Knight, 1920. This "dirty-white" strain is completely unrelated to any other used, having been bred from a wild mutant trapped in Illinois. CE/J mice have not been used in behavioral studies.

LP/J: Origin not known. These mice came to The Jackson Laboratory from Dunn in 1947 at generation 30. Little is known about this very long-lived agouti-piebald strain.

BALB/cJ: This strain originates from an albino stock acquired by Bagg in 1913. Subline c was established at generation 41 in 1947. This is a very aggressive albino strain with a very large brain, low activity, and about average learning ability for one- and two-way avoidance. About 20% of the animals have no crossing fibers in the corpus callosum.

Behavioral tasks

The battery of behavioral tests selected was designed to investigate performance on a number of tasks requiring different kinds of responses on the part of the animal. They were chosen in such a way as to cover as many facets of behavior as possible and to maximize differences between strains on individual measures. Wherever possible, we tried to use more than one test to tap each supposed basic behavioral dimension, to provide covariance for the planned correlations and factor analyses.

Well over 100 measures per strain were obtained from 15 separate behavioral tasks. Seventy-nine measures were employed in the final analyses on the basis of analyses of variance for strain differences and intra-task correlations between measures. Measures that did not show significant strain differences or that correlated >.9 with another measure from the same task were dropped.

The tasks can be divided into three general categories. A description of the categories and a rationale for using the various tests in each is given below. Complete details on apparatus, procedures, and measures obtained from each test are given in Appendix A.

Locomotor activity. Highly significant mouse strain differences have been found in almost every task that measures any kind of locomotor activity (e.g. Thompson, 1956; McClearn, 1959; Southwick and Clark, 1968; see also Wimer and Fuller, 1966). Such tasks are highly reliable and can be used to investigate a number of aspects of the response to a novel situation, e.g. amount of activity, latency of response, temporal changes in response, and eliminative behavior. Seven tasks, each measuring at least two aspects of locomotor activity, were included in the test battery. In the forced open field, animals were allowed to move around in a large square box for either two or five minutes for five consecutive days. In the free open field and emergence tests, mice could enter

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an open area or remain in a familiar enclosed space. Three other tests of activity were intended as controls for learning in tasks being performed in the same apparatus: spontaneous jumping in the active jumping box, stepping down in the passive jumping box, and barrier crossings in the shuttle box. All of these tests were run for several days, and measures of latency and/or amount of activity were taken.

The interpretation of locomotor activity as "exploratory behavior" has been of major theoretical concern to psychologists. Perhaps the most interest has centered around disagreements about the relationship between activity and emotionality or fear. While some contend that a novel situation evokes fear responses that compete with exploratory tendencies and thus reduce activity (e.g. Montgomery, 1955), others claim that the activity of an animal in a novel situation, particularly at first exposure, does not simply reflect exploratory behavior but is at least partly fear-motivated, i.e. is actually an attempt to escape (e.g. Welker, 1957). Several experiments (Welker, 1957; Glickman and Hartz, 1964) have demonstrated that rats are more active when the novel open-field type situation is forced upon them than in a situation in which they may choose to remain in an enclosure, supporting the fear-motivated activity hypothesis. Also in support are the results of a factor analytic study on rats (Whimbey and Denenberg, 1967) in which first-day activity was positively related to an emotionality factor (defined by defecation scores), while activity on subsequent days was negatively related. These investigators also found an independent exploratory activity factor, not loaded on emotionality, on which activity had a high positive loading on all days. Similarly, Wilcock and Broadhurst (1967) found that about half the covariance of ambulation in the open field loaded on a factor unrelated to emotionality. The other half of the covariance was negatively correlated with emotionality, but since these investigators conbined the results of four days of testing, it is not possible to isolate the potential early fear-motivated activity. In the mouse, on the other hand, it is not clear that any of the activity in the open field can be considered fear-motivated. Glickman and Hartz (1964) have shown that the "albino mouse" is less active in a forced situation than in a free one. In a factor analytic study employing five different tests of activity, McClearn and Meredith (1964) found that their ambulatory activity factor had negative or zero loadings for defecation, while the emotionality factor loaded zero on nearly all of the activity measures. McClearn and Meredith used genetically heterogeneous mice and single-day measures on each of the tasks, so the study provides no information on day-to-day changes in the factorial composition of activity.

It was hoped that the activity measures used in the present study would permit further analysis of exploratory behavior in the mouse as well as suggesting which components of activity are related to various aspects of the learning process.

Escape and avoidance conditioning. Significant mouse strain differences in learning have been found for active shock escape (R. Wimer et al., 1968), one-way active (Schlesinger and R. Wimer, 1967) and passive (Fuller, 1970) shock avoidance, and two-way avoidance (Royce and Covington, 1960; Collins, 1964). Our test battery employed two measures of shock escape,

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and one measure [illegible]each of the other behaviors. In one of the measures of active shock [illegible]pe, the mouse was required to jump to a shelf to escape foot-shock [illegible] the grid floor of a small box. When we found that some strains were much more likely than others to jump as a first response to foot-shock, we devised an additional task that required the animal to run down a runway to escape shock. The one-way active avoidance task was also performed in a runway, using light and tone as the stimuli to be conditioned. In the passive avoidance task, the mouse was required to remain on a shelf in order to avoid shock from a grid floor below. In all of these tasks, the measure used was latency of response and its changes from trial to trial. Measures of retention and extinction were taken in the passive avoidance task. Two-way avoidance performance was assessed in a shuttle box, in which measures of number of avoidances and number of inter-trial barrier crossings were taken. Number of trials to extinction was also measured.

The shock-escape tasks, requiring the mouse to learn to escape an unavoidable shock by moving to a "safe zone", were used here because they represent a simpler learning situation. We expected that all the strains would be able to reduce escape latency in a small number of trials, and that the more active strains would, in general, perform better. Avoidance conditioning is clearly more difficult for the mouse than simple escape learning. The particular avoidance tasks in the battery were used primarily because of current theories about the bases for performance differences between them, suggesting that strain-dependent differentials in performances could be related to underlying biological mechanisms.

With regard to the distinction between active and passive avoidance, it is currently believed that there are separate brain areas for control of the two kinds of response (Gerbrandt, 1964, 1965; McCleary, 1966); and Carlton (1963) has attempted to tie the two antagonistic systems to different neurotransmitter systems. A two-way avoidance task, in which the animal is required on a given trial to leave the safe area and return to a place in which it has been shocked previously, is thought to have both active and passive components. One-way active and passive and two-way avoidance are differentially sensitive to various lesions of the limbic system (McCleary, 1961; McNew and Thompson, 1966; Douglas, 1967; Liss, 1968; Van Hoesen, MacDougall, and Mitchell, 1969) and administration of psychoactive drugs (C. Wimer, Donner, and Martin, 1968; Fuller, 1970).

Discrimination learning and reversal. The discrimination learning tasks used in the present battery require the subject to respond consistently to one of two simultaneously presented stimuli. Such tasks have been shown to discriminate between inbred strains (R. Wimer and Weller, 1965) and between mice of high and low brain weight (C. Wimer and Prater, 1966; C. Wimer, Roderick, and R. Wimer, 1969). We have two two-choice maze devices for studying discrimination in the mouse. One requires the animal to swim to the correct arm in order to escape from the water. The second involves traversing an electrified grid and choosing the correct arm in order to escape shock. In both of these devices, the animal can be required to learn a spatial discrimination

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(choosing one side) or a visual discrimination (choosing black or white, lighted or dark). We used a spatial discrimination in the water maze and both a spatial and a visual in the runway T-maze for this test battery.

Once the animal has learned to choose one of two alternatives in either of the mazes, he can be required to perform a discrimination reversal, i.e., to respond to the previously unrewarded alternative. Prior to this study, no strain comparisons had been made for the reversal task, but there is evidence that mice can perform both spatial and visual reversals (C. Wimer, R. Wimer, and Roderick, 1971) and that high brain-weight mice perform reversals better than mice with average brain size (Elias, 1969). Mice were required to learn a discrimination reversal after each of the three tasks in our battery.

Discrimination learning tasks are generally thought to represent a more purely intellectual function than avoidance conditioning. Performance depends less on the animal's basic activity level and is in general more sensitive to lesions of the cerebral cortex (Galambos and Morgan, 1960). Discrimination reversal has long been used to study phylogenetic differences in intellectual abilities. Superior performance on a reversal task is thought to represent a flexibility that is valuable in adaptation to a changing environment (Bitterman, 1965). It is also clear that the neural mechanisms controlling reversal learning are at least to some extent distinct from those controlling discrimination learning, for animals with certain limbic lesions, especially in the hippocampus, show a severe deficit in reversals although they may be no different from controls in learning the original discrimination (Douglas, 1967).

In addition to the behavioral tests per se, we were interested in the temporal conditions of testing. Learning tasks with discrete trials can be administered with varying intertrial intervals. The distribution of trials that is optimal for learning has been suggested to be determined in part by rate and amount of permanent change per trial in the nervous system. Thus, strains of mice that differ widely in optimal temporal distribution of practice trials might also differ in the biological processes of memory trace formation, and this would permit the identification of extreme strains for the study of individual differences in physiological mechanisms underlying memory processes. Some strain differences in optimal distribution of practice have already been established (R. Wimer et al., 1968). In the present battery, we used a massed-trials and a distributed-trials condition for the passive avoidance task and for both active shock escape tasks.

Neurochemical procedures

It was our intention to investigate neurochemical mechanisms underlying the behaviors studied, with the purpose of eventually manipulating them pharmacologically in an attempt to modify strain-specific behavioral characteristics. To implement the first part of this program, measurements of amino acids and transmitter-related enzymes were taken on each of the seven strains. These measurements were carried out by members of the Division of Neurosciences at City of Hope, who had considerably more competence in the methods required than did the direct participants in the behavioral study.

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Dr. Geoffrey Tunnicliff, using micro-isotopic procedures developed by Dr. Richard E. McCaman, assayed at least four whole brains from each of the inbred strains for activities of the enzymes glutamic acid decarboxylase, choline acetylase, acetylcholinesterase, monoamine oxidase, and catechol-O-methyl transferase. Drs. Eugene Roberts and John Wein took brain extracts from four animals of each strain, removed the proteins, and analyzed the amino acids and related substrates in the extracts in an amino acid analyzer. This provided us with measurements of the levels of 26 amino acids.

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RESULTS

The first step in the analysis of the results was to subject the measures obtained in each behavioral task to analyses of variance, to obtain information about strain differences and interactions between strains and measures. We also ran correlations between the measures within each task. Measures that did not demonstrate significant strain differences or were highly correlated with other measures in the same task (indicating experimental dependence, a confounding variable in factor analysis) were either dropped from further analysis or were combined with the measures with which they were correlated. The final variables used in the factor analysis, together with a summary of analysis of variance results, are given in Table 1. The means for each strain on each of these 79 variables are given in Appendix B, Table B1.

It is clear from Table 1 that significant strain differences were found for nearly all the measures obtained, and there were a number of significant strain-by-condition interactions. In the context of this study, however, the analyses of variance were but a preliminary step.

In subsequent analyses, computing assistance was obtained from the Health Sciences Computing Facility, UCLA, sponsored by NIH Research Resources Grant RR-3. We next proceeded to a correlational analysis, calculating intercorrelations between all 79 measures, using the strain means as the basic data (thus n=7 for each correlation). The intercorrelation matrix is given in Appendix B, Table B2. There are a number of significant intra-task correlations, most notably between the various activity tasks, indicated that at least some of the strain differences are not task specific, but represent more general, basic, genetically-determined characteristics.

Next, the correlation matrix was factor-analyzed by the principle axis method and the first six factors, accounting for more than 99% of the total variance, were submitted to varimax rotation, which is a statistical approximation to "simple structure". The unrotated factor matrix for the first six factors, with eigen values for each factor, are shown in Appendix B, Table B3. All of the obtained communalities were greater than .99. The rotated matrix is shown below in Table 2. Decimal points are omitted in this and all correlation and factor matrices.

The identification and interpretation of the factors resulting from a factor analysis is a subjective process based on the patterning of the factor loadings, on our observations about the tests that have high loadings on particular factors, and on our ideas about what makes sense psychologically. On this basis, we have attempted to interpret the six factors. Only the first two could be identified with a reasonable degree of certainty. Some of the others appeared to be defined essentially by measures from a single task, suggesting that the experimental dependence resulting from the inclusion of more than one measure from the same task is affecting the results, although we eliminated or combined most measures with high intra-task correlations. For each factor given below, we have listed the factor loadings that affected our interpretation and followed the listing with our tentative identification of each factor.

Table 1: Variables used in the factor analysis (with abbreviations) and analysis of variance results

Task	Measure	Significance levels for strain main effects, simple main effects, and interactions
Five-minute open field: 5OF	A1: Squares entered on Day 1	.01
	A5: Squares entered on Day 5	.01
	A1-5: Habituation of activity	.01 for strain x day interaction
	D: Defecation, total for 5 days	.01
Passive avoidance latency: PJBL	1: Trial 1	ns
	5-1M: Learning measure, massed trials	.01 for strain x trial — strain x condition, .01
	5-1D: Learning measure, distributed trials	ns for strain x trial — strain x condition, .05
	RM: Retention trial, massed	.01 — strain x condition, .01
	RD: Retention trial, distributed	.05
	5-RM: Forgetting, massed (difference between trial 5 and retention trial)	.01
	5-RD: Forgetting, distributed	ns — strain x condition, .01
	E: Extinction trial	.01
	R-E: Extinction rate (difference between retention and extinction trials)	ns for strain x trial
Spatial discrimination, water maze: SWM	TCO: Trials to criterion, original learning	.01
	TCR: Trials to criterion, reversal	.01
	TCR-O: Negative transfer	ns for strain x task
	PEO: Perseverative errors original learning	.01
	PER: Perseverative errors, reversal	.01
	PER-O: Increased perseverative errors in reversal	ns for strain x task
	A: Number of alternations, 1st 30 free choice trials	.05
	TCF: Trials to fixation, free choice	.01
Two-minute open field: 2OF	A1: Squares entered on Day 1	.01
	A5: Squares entered on Day 5	.01
	A1-5: Habituation of activity	.01 for strain x day
	L1: Latency to leave 1st square, Day 1	ns
	L5: Latency, Day 5	ns
	L1-5: Decrease in latency over days	.05 for strain x day

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Step-down latency in passive jumping box, no shock, 5-day average: SDL		.01
Barrier crossings in shuttle box, no shock: SBA	1: Day 1	.01
	4: Day 4	.01
	1-4: Habituation of activity	.01 for strain x day
	$\bar{X}$: Mean number crossings	.01
Emergence test: E	PE: Percent of animals emerging	.01 (χ^2)
	L: Latency of emergence	.05
	A: Post-emergence activity, one minute	.01
	PR: Percent of animals retreating to enclosure	.01 (χ^2)
Active shock-escape, jumping box: AJB	PF: Percent of animals freezing on 1st trial	.01 (χ^2)
	L1: Latency, trial 1	.01
	L25M: Summed latency, trials 2 to 5, massed trials	.01 strain x condition, ns
	L25D: Summed latency, trials 2 to 5, distributed	
	L1-25M: Learning measure, massed	.01 for strain x trial, strain x trial x condition, .05
	L1-25D: Learning measure, distributed	.01 for strain x trial
Free open field: FOF	L1: Latency of emergence Day 1	ns
	L5: Latency, Day 5	ns
	L1-5: Decrease in latency over days	.01 for strain x day
	A1: Squares entered post-emergence, per minute, Day 1	.05
	A5: Squares entered, Day 5	ns
	A5-1: Increase in activity over days	.01 for strain x day
Two-way active avoidance: SB	LE: Escape latency, escape training trials	.05
	AV1: Number of avoids, trials 1-5	ns
	AV4-1: Number of avoids, trials 16-20 minus 1-5 (early improvement)	.01 for strain x trial
	AV6-4: Trials 26-30 minus 16-20; late improvement	
	ITC1: Number of intertrial crossings, trials 1-5	ns
	ITC3-1: Crossings, trials 11-15 minus 1-5	.01 for strain x trial
	AV/C: Avoids per intertrial crossing-efficiency of avoidance	.01
	ETC: Extinction, trials to criterion	.05
Spontaneous jumping latency: SJL	1: Day 1	ns
	5: Day 5	ns
	1-5: Decrease over days	.05 for strain x day
	$\bar{X}$: Mean across days	.01

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One-way active avoidance: AA	TC: Sessions to criterion	.05
	L: Mean latency, escape training	ns
Active shock-escape, runway: AR	PF: Percent of animals freezing on 1st trial	.01 (χ^2)
	L57M: Mean latency, trials 5 to 7, massed trials	ns } ns; strain x condition, .05
	L57D: Latency, trials 5 to 7, distributed	ns
	L1-57M: Learning measure, massed	} .01 for strain x trial; strain x trial x condition, ns
	L1-57D: Learning measure, distributed	
Spatial discrimination, T-maze: STM	TCO: Trials to criterion, original learning	.01
	PEO: Perseverative errors, original learning	.01
	A: Number of alternations, 1st 30 free choice trials	ns
Visual discrimination, T-maze: VTM	TCO: Trials to criterion, original learning	ns
	TCR: Trials to criterion, reversal	.01
	TCR-O: Negative transfer	.01 for strain x task
	PEO: Perseverative errors, original learning	} .05
	PER: Perseverative errors, reversal	
	PEO-R: Decreased perseverative errors in reversal	ns for strain x task
	FO: Percent side-fixation responses, original learning	} .01
	FR: Side-fixation responses, reversal	
	FO-R: Decrease in fixation responses in reversal	ns for strain x task

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Table 2: Rotated principal axis factor matrix

Behavioral measures		Factor Loadings					
		I	II	III	IV	V	VI
50F	A1	57	45	-11	-17	-65	01
	A5	82	40	-17	21	-25	-17
	A1-5	-71	-17	16	-52	-30	29
	D	-75	-52	23	10	23	-23
PJBL	1	12	-95	-09	11	03	-23
	5-1M	-40	-70	-17	55	04	-15
	5-1D	13	-32	-48	41	-03	69
	RM	-24	-89	30	-08	20	-12
	RD	00	-06	-61	63	30	-36
	5-RM	-13	39	-61	61	-12	-26
	5-RD	14	-33	84	-29	-21	17
	E	-35	61	-07	-10	23	66
	R-E	-96	10	-17	14	-03	-11
SWM	TCO	19	14	-79	-14	-25	-49
	TCR	-08	34	-89	24	-09	14
	TCR-O	06	23	-13	70	26	61
	PEO	08	79	-31	-51	01	14
	PER	-18	69	-49	-31	22	32
	PER-O	-41	-31	-52	39	54	12
	A	-11	-12	-88	-11	-18	40
	TCF	38	07	-89	-22	-04	07
20F	A1	57	43	27	02	-64	-00
	A5	68	16	25	30	-60	06
	A1-5	-28	65	03	-68	-08	-15
	L1	-50	-44	03	44	58	-14
	L5	-98	-09	-11	-12	00	-09
	L1-5	95	-01	12	22	14	09
SDL		52	-68	-19	05	15	-46
SBA	1	26	82	-13	06	37	-32
	4	-12	-19	-80	-01	-18	-53
	1-4	26	68	52	04	38	20
	X	05	26	-69	14	-01	-66
E	PE	93	10	-06	-08	-33	-10
	L	33	-02	20	24	80	40
	A	24	57	20	69	-18	-26
	PR	-39	06	06	-80	39	24
AJB	PF	-15	49	29	39	65	28
	L1	-28	60	26	-70	05	-04
	L25M	-16	41	06	85	26	10
	L25D	-12	-01	-29	92	-24	01
	L1-25M	03	-10	00	-96	-24	-06
	L1-25D	-18	42	27	-84	01	-05

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FOF	L1	-07	-91	25	-11	29	-12
	L5	-89	-25	-12	-25	-24	-13
	L1-5	65	-54	30	11	42	01
	A1	44	69	-05	29	-44	24
	A5	87	20	17	-06	-39	-09
	A5-1	31	-68	24	-43	18	-40
SB	LE	-39	-82	13	-20	33	-08
	AV1	04	10	24	30	-86	31
	AV4-1	-05	40	13	14	-58	68
	AV6-4	-43	-04	32	12	80	-23
	ITC1	-36	08	18	09	-82	-38
	ITC3-1	-66	07	-61	-17	-39	02
	AV/C	30	19	18	19	-17	88
	ETC	54	-37	72	-22	02	00
SJL	1	-18	24	06	71	-05	63
	5	-55	03	33	-10	76	-07
	1-5	30	13	-20	53	-60	46
	X	-64	-00	11	47	28	52
AA	TC	-19	-94	12	15	09	-17
	L	-09	-78	28	-23	44	-22
AR	PF	-20	-70	60	-24	21	09
	L57M	-82	37	38	-19	10	-00
	L57D	-08	-42	15	09	88	09
	L1-57M	36	-22	89	-16	-08	04
	L1-57D	-32	-23	74	-26	-40	26
STM	TCO	-96	-11	-13	06	-20	05
	PEO	-93	14	00	14	08	29
	A	06	-15	35	72	-56	14
VTM	TCO	-95	-04	24	-06	12	-16
	TCR	-36	29	11	-56	04	67
	TCR-O	15	32	-02	54	-03	76
	PEO	-59	-14	-38	65	27	-02
	PER	-71	13	27	09	25	58
	PEO-R	21	-24	-58	45	-02	-59
	FO	-87	-20	-23	18	33	02
	FR	-57	16	-02	09	20	78
	FO-R	-38	-39	-23	10	16	-78

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Factor I

Measure	Task	Loadings Day 1	Day 5
Activity	5-min. open field	57	82
	2-min. open field	57	68
	free open field	44	87
Latency	2-min. open field	-50	-97
	free open field	-07	-89
	spontaneous jumping	-18	-55

Factor I has tentatively been identified as maintenance of locomotor activity. It apparently reflects the animal's activity after he has become familiar with a novel situation, for the Day 5 loadings are consistently higher than those for Day 1. Another variable that loads high on this factor is the difference between retention and extinction latencies in the passive jumping box (-.96): this suggests that strains with high "activity maintenance" also maintain passivity, i.e. after shock is turned off, they are less likely to decrease their latency than are strains with lower activity maintenance. In fact, however, the strains that were high on Factor I did relatively poorly in passive avoidance, and their retention latencies were already quite low. In most cases, their extinction latencies were lower than strains low on the factor. Also loading high are Day 1-to-5 decrease in latency in the 2-minute open field (.95), indicating an increase in activity (shorter latency) over time; percent of animals emerging from an enclosure into an open arena in a single trial (.93); and latency in later trials in runway shock escape (-.82). All of these are consistent with our interpretation of the factor. Significant negative loadings were also found for both trials to criterion and perseverations to a side in the original learning of the spatial and visual T-mazes (ranging from -.87 to -.96); this suggests that high continued activity facilitates discrimination learning reinforced by escape from shock and requiring an active response. Note that defecation has a high negative loading (-.75). Apparently, in this case, emotionality interferes with locomotor activity.

Factor II

Measure	Loading
Trial 1 step-down latency in passive jumping box	-95
Day 1 barrier crossings in shuttle box (no shock)	82 (Day 4, -19)
Activity, emergence test	57
Day 1 latency, free open field	-91 (Day 5, -25)
Day 1 activity, free open field	69 (Day 5, 20)
Average escape training latency (Day 1), shuttle avoidance task	-82
Average latency, 1-way runway avoidance	-78
Percent freezing, runway shock-escape, trial 1	-70

On the basis of these loadings, we interpreted Factor II as reflecting initiation of activity in an unfamiliar situation. Latencies on initial

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trials have very high negative loadings (low latency=high activity), particularly in "free" tasks, where the animal may choose to remain in a relatively safe, familiar situation. Also loading high are latencies on tasks requiring the animal to run to escape or avoid shock. Supporting our previously-mentioned suspicion that jumping is dependent on factors other than those controlling general locomotor activity is the fact that latency in the active jumping box has a high positive loading (.60) on this factor: the more active strains frequently ran around the grid floor in response to shock, but failed to jump to the shelf. Defecation has a negative loading (-.52) on this factor as well as on Factor I. It is apparent that, in the mouse, both of these relatively independent aspects of locomotor activity are negatively correlated with emotionality.

In this factor analysis, Factors III, IV, V, and VI were defined by, respectively, the spatial water maze, the active shock-escape task in the jumping box, shuttle avoidance, and the T-maze visual discrimination task. It is apparent that strong interrelations within these tasks are producing task-specific common-factor variance. In subsequent analyses, which included the biochemical measures, some of these highly intercorrelated measures were dropped, primarily because the computer program limited us to 80 variables per analysis, and the factor structures that emerged were somewhat different, as will be discussed below.

The next step in the analysis was a strain comparison for the five enzymes related to putative neurotransmitters that had been assayed: glutamic acid decarboxylase (GAD), choline acetylase (ChAc), acetylcholinesterase (AChE), monoamine oxidase (MAO), and catechol-O-methyl transferase (COMT). The means for each strain on each of the enzymes are shown in Table 3, together with the correlations between the enzymes, and the F-ratios and significance levels obtained from the five one-way analyses of variance. The strains were significantly different on all of the enzymes. Correlations between enzyme activity levels and the behavioral measures are given in Appendix B, Table B4.

A second factor analysis was carried out, adding the five enzymes and dropping four behavioral measures. All of the enzymes had obtained communalities of >.99. In the resultant rotated factor matrix, the first two factors, as defined above, were readily identifiable. The loadings of the enzymes on these two factors are given below.

	Factor I Maintenance of Activity	Factor II Initiation of Activity
GAD	-54	-20
ChAc	-86	-17
AChE	15	-07
MAO	79	-33
COMT	-29	-09

It is apparent that ChAc, and to a lesser extent GAD, are negatively related to long-term locomotor activity, while MAO is positively correlated. None of the enzymes appears to be a factor in the initiation of activity.

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Table 3: Mean whole-brain levels of enzyme activity (in μmoles/mg. protein/min.), results of analyses of variance for strain comparisons, and correlations between enzymes

Strains		Enzyme GAD	ChAc	AChE	MAO	COMT
C57BR/cd		.444	2.10	3160	45.2	.970
C57BL/6		.415	2.14	3000	39.9	1.230
DBA/2		.476	2.44	3850	35.5	.872
CE	Means	.451	1.71	3380	39.0	1.110
CBA/Ca		.464	2.11	3400	47.2	.902
LP		.473	2.42	3440	32.5	.803
BALB/c		.477	2.78	3160	30.1	1.274
	df	6/35	6/43	6/38	6/43	6/43
	F	8.47	3.23	4.91	7.57	8.36
	P<	.01	.05	.01	.01	.01
Inter-correlations	GAD		56	66	-48	-43
	ChAc			09	-68	06
	AChE				-17	-69
	MAO					-20
	COMT					

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In this analysis, Factors III-VI, which were defined by specific tasks, also emerged again, although in a different order. The only one of them that produced significant loadings for the enzymes was III (formerly Factor IV), on which the loadings were as follows:

GAD	71
ChAc	29
AChE	96
MAO	26
COMT	-77

This is the factor previously defined by the active shock-escape task in the jumping box, in which trial 1 latency is negatively correlated, latency on later trials positively correlated, and the improvement over trial 1 negatively related. That is, strains that are high on this factor tend to escape shock by jumping quickly (low latency) on the first trial, but not to improve with practice. AChE and GAD have high positive loadings, and COMT has a high negative loading on the factor, which may represent some active form of emotional reactivity.

The 26 amino acids were analyzed next. The strain means for four brains per strain are given in Appendix B, Table B5. Analyses of variance for strain comparisons were not calculated for these data. Instead, they were factor analyzed together with 54 of the behavioral measures. Since 25 of the behavioral variables had to be eliminated for this analysis, it was expected that the factorial structure would be somewhat different from that of the previous two analyses. That is, since most of the covariance produced by interdependence of measures from the same task should disappear, some of the factors might be defined by amino acid clusters rather than by behaviors.

The rotated factor matrix is shown in Table 4. All communalities were $>.99$. Again, six significant factors were obtained, and in fact several of them were identifiable as corresponding to factors defined in the analysis of behaviors alone.

Factor I is similar to the previous Factor III, which was defined by spatial discrimination in the water maze. In this analysis, it appears that the latter may be a more general learning factor, having high negative loadings on such measures as trials to criterion in the spatial water maze and perseverative errors in the T-maze visual discrimination, and high positive loadings for latency reduction in the runway shock-escape task. By no means, however, do all of the learning measures load significantly, and the loadings for a given task are very variable. All of the open field measures have essentially zero loadings. A number of the amino acids have reasonably high loadings on this as yet undefined learning factor. Most notable are the high positive loading for carnosine (+.80) and the negative loadings for tyrosine (-.85) and methionine (-.85). These three amino acids together account for less than one per cent of the total amino acid pool. Of the more prevalent substances, only taurine, .52, and phosphoethanolamine, -.63, have loadings $>.5$.

Factor II resembles former Factor V (reflected), defined by shuttle

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Table 3: Rotated principal axis factor matrix for behavioral measures and amino acids

	Measure	Factor loadings I	II	III	IV	V	VI
5MOF	A1	03	32	89	-08	29	-10
	A5	-21	-08	92	-18	06	25
	A1-5	38	48	-53	20	20	-51
	D	04	18	-88	07	-43	04
PJBL	1	-21	-13	-12	16	-89	-32
	5-1M	-38	00	-55	-31	-65	-17
	5-1D	-30	-49	00	-50	01	-65
	RD	-87	-23	-12	-25	-20	27
	5-RD	91	08	08	10	-36	-14
	E	18	-21	-29	-20	89	-08
SWM	TCO	-81	30	40	28	10	-03
	TCR-O	-10	-58	-08	-76	28	-01
	PEO	-07	07	30	31	90	07
	PER	-25	-12	-05	15	95	-03
	PER-O	-59	-43	-66	-14	-06	-11
20F	A1-5	17	45	-00	49	70	20
	L1	-22	-29	-80	-12	-41	20
	L5	-14	47	-85	08	13	-08
	L1-5	10	-58	74	-12	-24	14
SDL		-35	-26	27	33	-79	-03
SBA	1	-25	-15	29	08	52	74
	4	-89	34	02	24	-15	-12
	1-4	52	-36	18	-13	46	58
E	PE	-01	-09	99	06	-12	-02
	L	20	-94	-10	-09	02	21
	A	-06	13	37	-65	05	64
AJB	L1	42	32	-09	49	65	23
	L25D	-49	06	-06	-85	-18	04
	L1-25M	26	33	17	80	14	-36
FOF	L1	16	-23	-39	34	-78	-21
	L1-5	22	-68	24	14	-64	06
	A1	02	09	69	-54	47	10
	A5	20	01	97	-02	-10	09
	A5-1	18	-10	09	68	-70	-04
SB	AV1	30	48	35	-68	00	-32
	AV4-1	37	20	21	-63	50	-37
	AV6-4	10	-32	-73	17	-10	56
	ITC1	05	95	05	-25	-14	02
	ITC3-1	-48	56	-35	02	37	-43
	AV/C	45	-37	29	-56	34	-39
	ETC	71	-22	35	22	-52	03

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SJL — 1	08	-23	-18	-91	26	-09
SJL — 5	22	-26	-79	27	10	42
AR — PF	60	-13	-45	28	-56	-19
AR — L57M	36	39	-68	04	42	27
AR — L57D	06	-74	-55	20	-29	16
AR — L1-57M	86	-06	25	07	-42	11
STM A	20	22	16	-85	-40	-07
VTM — TCO	13	41	-89	06	06	15
VTM — TCR-O	41	-24	20	14	70	-47
VTM — PEO	-56	-09	-68	-45	-07	06
VTM — PER	38	-10	-76	-30	40	-11
VTM — PEO-R	-85	03	19	-07	-46	17
VTM — FO-R	-54	30	-42	29	-52	29
Cysteic acid	-14	-04	15	-97	-01	-06
GPE	28	63	-21	51	45	-11
OPE	-63	59	21	-34	28	12
Taurine	52	-17	28	-09	78	03
Aspartic acid	-19	68	-62	22	26	-01
Serine	-20	-46	-41	25	22	68
Threonine	-53	56	-49	16	00	37
Glutamic acid	-44	81	02	18	-16	-29
Glutamine	31	77	19	14	33	-37
Half-cysteine	-36	20	10	87	-10	23
Glycine	06	18	16	-57	75	-23
Alanine	10	81	-54	11	-12	-15
Cystine	66	-30	07	-48	27	41
Valine	-38	32	-14	45	34	63
Methionine	-85	-12	12	-29	-37	13
Isoleucine	15	89	-16	12	-00	38
Leucine	-36	17	28	-86	03	11
GABA	02	31	-25	41	81	14
Tyrosine	-85	05	45	-08	-23	-10
Phenylalanine	-19	73	-29	12	58	-02
Histidine	61	30	-28	-25	56	29
Ornithine	14	-62	-19	-03	74	14
Lysine	53	31	33	-31	46	45
Ethanolamine	01	-38	-16	02	05	91
Arginine	-08	-27	55	-58	-38	37
Carnosine	80	48	02	11	32	-11

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avoidance, but is primarily defined by the biochemical variables, and appears to be a general amino acids factor. Glutamine, glutamic acid, alanine, and isoleucine are all very highly positively associated, and six other substances have loadings $>.5$. The substances with high positive loadings, taken together, account for 64% of the total amino acid pool. It is not possible to identify this factor behaviorally as yet.

Factor III appears to be the maintenance of activity factor, and does not have any amino acid loadings $>.75$.

Factor IV has significant negative loadings for cysteic acid and leucine, and a positive loading for half cysteine. The behavioral interpretation is not clear, for the pattern of loadings is quite ambiguous.

Factor V is interesting because of high positive loadings for two important amino acids, taurine and GABA. Behaviorally, it is similar to the previous Factor II, suggesting that these two amino acids are positively related to the initiation of activity.

Factor VI is uninterpretable except for having a very high loading for ethanolamine.

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DISCUSSION

The original goals of the research project were to identify and characterize some independent genetically associated factors producing individual differences in learning and memory, and to search for relations between those factors and various aspects of brain chemistry.

Examination of Table 1 will reveal that we did in fact find a number of genetically associated differences in learning- and memory-related tasks. However, our factor analyses revealed two major independent behavioral factors, neither of which was defined by learning and memory variables. Instead, both were related to aspects of activity. This suggests that much of the genetically associated diversity in learning performance which has been observed both by us and by others may be due to genetically associated diversity in aspects of activity which appear to be involved in all learning tasks. If initiation and maintenance of activity are the two principal dimensions of genetically associated behavioral variation which are presently available to us (and most likely, to others as well) for study with behavioral tasks, then these factors should clearly be explored thoroughly before moving on to possible learning factors which are less pervasive and more task-specific. Therefore, the remainder of this Discussion, and the primary conclusions resulting from this study, are concerned with aspects of activity, and not with learning and memory as originally intended.

Behavioral Analyses

The two activity factors, initiation and maintenance, are somewhat different from those found by previous investigators. McClearn and Meredith (1964), also using mice, found a single ambulatory activity factor which was independent of their emotionality factor. That they failed to extract two activity factors is probably explainable by the fact that they used only one-trial measures on their activity tasks, while our failure to find an independent emotionality factor is due to our use of only one measure of "emotionality", i.e. defecation in the open field. Studies on the rat have typically found two activity factors, generally one negatively related to emotionality and one unrelated (e.g. Wilcock and Broadhurst, 1967). Whimbey and Denenberg (1967), however, found that early activity had a positive emotionality loading while later activity loaded negatively. This is in contrast with our factors, both of which were negatively related to emotionality. This contrast is consistent with other evidence (e.g. Glickman and Hartz, 1964) suggesting that there may be a species difference: while initiation of activity may be partially fear-motivated in the rat (Welker, 1957), it does not appear to be so in the mouse. Hayes (1960) has pointed out that, to the extent that activity is fear-motivated, there should be a negative correlation between activity in the free and the forced open-field situation, i.e. that the animal which is most fearful and therefore most active in a non-escape situation should be most likely to stay in a safe place when it is provided. However, he found a positive correlation of .64 between the two situations, thereby failing to confirm Welker's hypothesis even for the rat. In our experiments, the correlations between free and forced (5-minute) open field activity were .81 for Day 1 and .86 for Day 5, confirming Hayes conclusion. It appears, then, that - for the mouse - locomotor activity can be separated into two orthogonal

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dimensions, one relating to the initiation of activity in a novel situation and the other to the maintenance of activity once the situation has become more familiar. The maintenance factor is apparent in both free and forced situations and has a higher emotionality loading than the initiation factor, which is more clearly related to free situations in which more variability of initial latency is possible.

The escape and avoidance conditioning tasks were, as expected, related to both activity factors. However, the escape tasks were surprisingly less related to the activity factors than the one-way avoidance tasks. The initiation factor accounted for almost all of the between-strain variance in most of the measures of both passive and one-way active avoidance. Two-way shuttle avoidance, while it had some strong components on the two major activity factors, defined another factor which also had moderate loadings on some activity measures. Although this factor was not, unfortunately, identifiable from this study, the results support the current belief based on lesion studies that two-way avoidance is functionally separable from one-way active and passive.

Discrimination learning and reversal learning were expected to depend less on the animal's basic activity level. Contrary to expectation, however, performance in both a spatial and a visual discrimination in the T-maze had high positive loadings on the maintenance factor, suggesting that a consistently fast running response is a considerable advantage in these tasks or that activity and discrimination learning are both in part a function of the same central process. The expected differences between original discrimination learning and reversal learning were not immediately apparent. In general, measures taken from original learning for a task loaded on the same factor as reversal measures for that task. For the visual discrimination, however, there was an additional factor that appeared to load primarily on reversal measures and on the difference between acquisition and reversal performance. This factor had zero loadings for all of the activity measures, and was defined by avoidances per inter-trial crossing in shuttle avoidance, which is perhaps the best "pure" learning measure for that task. This factor, then, may represent a more purely intellectual function, independent of activity level. It is not fully interpretable from the present analysis, but certainly deserves further investigation.

No conclusions can be drawn about memory trace formation as reflected in optimal temporal distribution of practice, for the factor loadings for massed vs. distributed trial conditions do not show any consistent pattern.

Relations With Brain Chemistry

What can be said about the biological nature of the behaviors studied, based on the loadings of the neurochemical measures on the two major behavioral factors? Factor I, maintenance of locomotor activity, is related to three of the transmitter-related enzymes, but not to any of the amino acids. According to the results of the factor analysis, a strain of mice which has a high level of choline acetylase (ChAc) tends also to have a high level of glutamic acid decarboxylase (GAD) and a low level of monoamine oxidase (MAO). Loadings of these three enzymes on maintenance of

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activity factor were as follows: ChAc (-.86), GAD (-.54), and MAO (+.79). Thus, these mice will tend to maintain a high level of activity over long periods in such situations as the open field, and will generally be superior in learning tasks requiring an active response.

Factor II, on the other hand, is unrelated to the enzymes measured, but has high positive loadings for the amino acids taurine, γ-aminobutyric acid (GABA) and glycine. The loadings of these amino acids on the initiation of activity factor were as follows: taurine (+.78), GABA (+.81), and glycine (+.75). A strain having a high level of one of these will tend also to be high on the others. These mice will be quick to initiate activity in a novel situation, and will perhaps not do as well on tasks requiring a long series of trials. Interestingly, all of these three amino acids have been considered as possible inhibitory neurotransmitters (Curtis and Johnston, 1970)

Constellations of Characteristics

A secondary objective not mentioned heretofore in this report was that we hoped to be able to describe the mouse strains as individuals on the basis of their scores on key variables related to our obtained factors. Such characterizations could be useful in testing hypotheses about human behavior, hypotheses concerning motivation, learning ability, and personality and their biological bases. Two of the strains, CBA/CaJ and BALB/cJ, can be clearly characterized by the present analysis. BALB/cJ could be called a low-maintenance strain: while not particularly slow to respond in a novel situation, BALBs do not maintain a high level of responding over repeated trials and habituate much more rapidly than the other strains, particularly where ambulatory activity is involved. They do very poorly in learning tasks involving an active running response, although not so badly where a jumping or swimming response is required. They are a highly emotional strain as defined by defecation in the open field. With respect to the enzymes correlating highly with the maintenance factor, BALBs have a very high ChAc level and a very low level of MAO, and a GAD level among the three highest strains.

CBA/Cas, unlike BALBs, seem to maintain exploratory activity fairly well once they initiate it, but they are very slow starters. Also a highly emotional strain, they have high latencies in novel situations, but latency decreases (and activity increases) as the situation becomes familiar. They tend to do fairly well in most of the learning tasks. Their scores are about average on the enzyme measures (except that they are high on MAO), but their values are very high on the three amino acids that appear to be related to activity initiation: taurine, GABA, and glycine.

While CBA/Cas and BALBs strains represent "lows" on each of the major factors, there are no clear "high" strains, although CE/J is closest to being a high maintenance strain. LP/J is, interestingly, quite high on the initiation factor but almost as low as BALB/cJ on maintenance: a fast starter that appears to give up fairly easily.

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CONCLUSIONS

The primary conclusions resulting from this study of the behavior and brain chemistry of seven inbred strains of house mice are as follows:

1. Behavior. There are two major general factors involved in producing genetically associated differences in many mouse behaviors, including behaviors generally presumed to be related to processes of learning and memory. These factors have been named by us to be (1) initiation of locomotor activity and (2) maintenance of locomotor activity.

2. Relations between brain chemistry and behavior. It appears very likely on the basis of our work that there are relations between some specific classes of neurotransmitter systems in the mouse brain and some specific classes of behavior. Strong functional relations suggested by our findings are between choline acetylase and monoamine oxidase (enzymes related to acetylcholine and norepinephrine, respectively) and maintenance of activity; and between the two putative inhibitory neurotransmitters, taurine and gamma-aminobutyric acid, and initiation of activity.

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APPENDIX A: APPARATUS AND PROCEDURES

General laboratory and experimental procedures

The principles for the care and use of animals as approved by The American Psychological Association were followed at all times. Standard precautions were taken against contamination and disease. Animals received from The Jackson Laboratory were housed in groups of about 5 (with the exception of the strain BALB/c mice, which were housed individually because of fighting) in disposable cages with sawdust (originally sterolit) as the bedding material. Food and water were available ad lib; 1/2 ml of terramycin per liter was added to the water for 2-5 days after arrival.

Mice were transported between housing and experimental areas in 32 oz. ice cream cartons or 16 oz. glass jars with bakelite lids. In general, animals were left in their transport containers 30 to 60 min. both before and after each experimental session. Designs for all experiments were carefully balanced to control for irrelevant effects.

Apparatus

The 15 behavioral tasks were carried out in five basic pieces of equipment, with modifications and/or procedural variations appropriate to the specific task. The five devices are described below, together with the tasks for which they were used.

Open field. The open field was a 25 x 25 x 12 inch high open wooden box with a white floor marked off into 25 5-inch squares. Auxiliary equipment consisted of Meylan timers for timing sessions and measuring latency, and hand counters for tabulating number of squares entered. The apparatus was used to measure free and forced open-field behavior, and for the emergence test.

Jumping box. The jumping box was a 7 x 7 x 7 inch translucent plastic box, with an electrifiable grid floor mounted one inch above the base. Two kinds of shelves could be mounted in the inside of the box. The "active" shelf was 1 1/2 inches wide, and ran completely around the inside wall 2 5/8 inches above the grid floor. The "passive" shelf was one inch wide and 5 3/8 inches long, and was inserted along one wall only, one inch above the floor; this shelf could be rotated about a pivot point at one end so that it lay flat against one of the walls of the box when in a vertical position in order to prevent escape from shock once the animal descended. Auxiliary equipment consisted of a Grason-Stadler shock scrambler, Meylan timers for measuring latency and duration of shock, an oscilloscope and NE-2 bulb for checking shock level. This apparatus, with appropriate shelf attached, was used to measure active shock escape and passive shock avoidance, as well as spontaneous jumping and stepping down.

Water maze. The water maze apparatus is shown in Figure A1. (The lights shown in the figure were not used in this study.) It was constructed of galvanized sheet metal and was 10 inches high. It was sub-

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merged in about 6 inches of water at about 25° C. A translucent plexiglas platform in the start area could be raised and lowered; at its maximum height it was 6 inches above the bottom of the maze, just at the surface of the water. A plastic gate, which could be lowered to prevent movement between the start area and the arms of the maze, permitted the mouse to see the choice point from the start platform. A mesh ladder, which permitted escape from the water, could be placed at the end of either or both arms; a dummy ladder, too high for the mouse to reach, could be placed at the end of an arm from which the mouse was not intended to escape. Stop watches and Meylan timers were used to measure latencies and to time the trials. This apparatus was used to measure spatial discrimination learning and reversal.

Shuttle box. The shuttling device was a Lehigh Valley toggle-floor shuttle box for mice with auxiliary shock source, counters, timers, etc. The two sides of the cage were separated by an opaque barrier with a hole through which the mouse could jump. Lights mounted at either end of the box were used in conjunction with a 15 KHz tone as conditioned stimuli. Shock was set at .4 ma. This apparatus was used to measure spontaneous shuttling activity and two-way active avoidance.

Runway T-maze. The apparatus that was used for both straight runway and T-maze tasks is shown in figure A2. It was constructed of 1/4 inch thick black plexiglas, and had a grid floor and a wooden base. For runway conditions, a goalbox with removable wooden escape ladder was placed at the end of the runway; goalboxes were used at the ends of both arms for the maze conditions. Auxiliary equipment included a Grason-Stadler shock scrambler set at .2 ma, a Meylan timer for measuring latencies, tone generator and lights, and associated Lehigh Valley electronic programming equipment. This apparatus was used for active shock escape, one-way active avoidance, and both spatial and visual discrimination learning and reversal.

Procedures: Locomotor Activity

Five-minute open field. For this forced open-field task, the mice were run in the open field for 5 minutes each day for 5 consecutive days. The animal was placed in a corner of the field, and cumulative number of squares entered was recorded at the end of each minute. Number of urinations and defecations was also recorded.

Two-minute open field. The mice were run in the open field for 2 minutes each day for 5 consecutive days. Measures recorded were total number of squares entered in each 2-minute period, and latency of leaving the first (corner) square.

Free open field. The open field apparatus was used, but a corner square was modified by the addition of a holder for the animal's transport carton. The mouse, in his carton, was placed in the corner holder. After 5 minutes the carton lid was removed and the mouse was free to emerge, explore, and return to the carton during a 10-minute period. The entire procedure was repeated for five consecutive days. Measures recorded included latency of first emergence from carton, number of returns to carton, total time in carton,

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number of squares entered in open field, and number of defecations.

Emergence test. The standard open field was modified by eliminating one row of 5 squares, replacing them with a plastic chamber. After familiarization in the chamber, the mouse was permitted to emerge, and--subsequent to his emergence--was allowed to explore for 60 seconds. Latency of emergence, number of squares crossed, and number of retreats to the chamber were recorded. Just one session was run on this task.

Shuttle activity. The shuttle box apparatus was used for this task, but the grid floor of the box was not electrified. The mouse was placed in one side of the box and allowed to cross at will for 5 minutes. The test was repeated for a total of 4 consecutive days. Number of barrier crossings per session was recorded.

Spontaneous step-down. The jumping box with the "passive" shelf was used. The mouse was placed on the shelf and allowed to step down spontaneously; when he did so, the shelf was raised and the animal was removed from the box. Mice were run for a total of 5 trials under either a massed (20 sec. intertrial interval) or a distributed (24 hrs. between trials) condition. Latency of stepping down was recorded for each trial.

Spontaneous jumping. The jumping box with the "active" shelf was used. The mouse was placed on the (non-electrified) grid floor of the box and allowed to jump or climb to the shelf. If the animal did not reach the shelf in 3 minutes, the trial was discontinued. Animals were run one trial a day for 5 days, and time to ascend to shelf was recorded on each trial.

Procedures: Escape and avoidance conditioning

Active shock-escape jumping box. The active jumping box was used for this task. After 60 seconds of familiarization on the shelf and grid floor, .25 ma shock was turned on while the mouse was on the floor and latency of escape to the shelf was recorded. Shock intensity was reduced to .20 ma on subsequent trials. Animals were run for 5 trials under either a massed (intertrial interval of about 15 seconds) or a distributed (24 hrs. between trials) condition.

Active shock-escape, runway. A goal box was placed at the end of the runway section of the T-maze. The mouse was placed in the start area and the shock scrambler was immediately activated. Time to escape to the top of the ladder at the back of the goal box was recorded. The animals were given 10 massed or distributed trials. The massed trials had an intertrial interval of about .1 min., which was possible because a second experimenter was recording latencies. The distributed trials were run one trial a day, 5 days a week; thus, the intertrial interval was approximately 24 hours, except that 72 hours elapsed between trials 5 and 6.

Passive avoidance. The jumping box with rotating shelf was used for this task. The animal was placed on the shelf and allowed to step down onto the grid floor. When he stepped to the floor, the shelf was retracted and .1 ma shock was administered to the feet for .07 minutes. Mice were run for up to 5 trials, under either massed (20 second inter-

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trial interval) or distributed (24 hour interval) conditions. When a mouse reached a criterion of 3 minutes on the shelf on any trial, he was removed from the box and testing was discontinued. One week after completion of the learning task, animals were given one retention trial, during which shock was not turned on. On the following day, one extinction trial was given. Step-down latency was recorded on all trials, except that animals reaching criterion before trial 5 were assigned a score of 3 minutes for the remainder of the learning trials.

One-way active avoidance. The runway portion of the T-maze, with goal box and ladder, were used for this task. Prior to the start of avoidance conditioning, all mice were given 10 massed escape trials. In this series the animal was placed in the start area with the gate to the runway closed. The gate was opened and the shock turned on after 15 seconds. Latency of escape to the ladder was recorded. Avoidance training was begun on the following day. Again the animal was placed in the start area, and after 15 seconds the gate was opened, at which point a light and 15 KHz tone were turned on. These conditioned stimuli were followed (at a random interval averaging 5 seconds) by foot shock. The mice were run for 10 trials a day to a criterion of 18 shock avoidances out of 20 trials on 2 consecutive days. Number of avoidances was tallied as well as escape latency on non-avoid trials. On the day after an animal met the avoidance criterion he was run on extinction. The same procedure was used except that the shock was disconnected. Noise associated with turning on the scrambler remained and light and tone were left on for the entire trial. Animals were run on extinction for 5 days (50 trials). On any trial, if the animal had not climbed the ladder at the end of 3 minutes, he was started on a new trial. Time to ladder was recorded on all trials. (This measure was not used in the final analysis due to procedural and scoring ambiguities.)

Two-way active avoidance. This task was run in the shuttle box. The mice were first run on 10 (massed) trials of escape training with the light and 15 KHz tone disconnected. Escape latency was recorded for each trial. Avoidance conditioning was begun on the next day. The animal was placed in one side of the box, and after 45 seconds the first trial was begun. A trial consisted of presentation of the conditioned stimuli, followed at a random interval, varying from 3 to 7 seconds and averaging 5 seconds duration, by footshock. When the mouse crossed the barrier, shock, light and tone were terminated. The next trial began 60 seconds later. Animals were run for ten trials a day to a criterion of 18 avoids out of 20 trials on two consecutive days. Measures recorded during this phase were number of avoids and number of intertrial crossings per day, and cumulative escape latencies over a 10-trial session. Extinction was begun on the next day following attainment of the acquisition criterion, and was run 10 trials a day until the actual number of "avoids" on a given day was less than the number of avoids expected by chance (based on total number of crossings). During extinction the light and tone went on at 60 second intervals, (determining the start of a trial) but shock was never administered. Measures recorded during this phase were the same as for the avoidance phase, with an "avoid" defined as a crossing within 5 seconds of light and tone onset.

Procedures: Discrimination learning and reversal

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Spatial discrimination, water maze. Animals were given 3 massed familiarization trials with an escape ladder placed across the choice point area before starting discrimination training in the water maze. As in all trials, the mouse was placed in the water near the platform seat, with the gate down, and allowed to climb onto the seat. After 20 seconds, the gate was raised and the seat lowered, forcing the mouse to swim until he reached the escape ladder. The free choice phase was started on the day following the familiarization trials. In this phase, ladders were placed at the ends of both arms, so that the animal could escape from either side. Four days of free choice were run under a distributed condition of practice, 5 trials a day with a 10-minute intertrial interval. All subsequent trials were massed, separated by about 20 seconds, and 5 trials a day were given in all phases. Beginning at trial 21, animals were continued on free-choice trials until they reached a "preference criterion" of swimming to one side on 9 our of 10 trials on 2 consecutive days, or for a maximum of 50 trials. After criterion was met (or on trial 51), original learning began. In this phase, the mouse was trained to escape via the arm that was least preferred during the free-choice trials. Reversal training was begun when the subject swam to the correct arm on 9 out of 10 trials on two consecutive days. In this last phase, the animals were trained to swim to the side of original preference, the non-reinforced side during original learning. The criterion was the same as for original learning. Direction of choice was recorded for each trial.

Spatial discrimination, T-maze. This task was similar in design to the water-maze task described above, but escape from shock rather than from water was the reinforcement. On all trials the mouse was placed into the start area, the start gate was raised and shock turned on; the subject ran to the goal box and escaped up the ladder. In runway familiarization, the first phase, the animals were given 10 massed trials (intertrial interval of about .10 minute) each day for four days on the straight runway with the goalbox placed at the end of the runway. Then began the free-choice phase, with the arms of the T-maze opened and goal boxes with ladders placed at the end of each arm. The mouse could escape from either arm during this phase. Animals were given 5 distributed trials (10-minute intertrial interval) a day for four days, followed by 5 massed trials (.20 min. interval) a day for the remainder of the task. Criteria for free choice, original learning, and reversal were the same as for the water maze. Direction of choice and latency were recorded for all trials. (The latency data were not used in the final analysis.)

Visual discrimination, T-maze. This task was run in the T-maze, with flashing lights added in the arms of the maze (see Fig. A2). The general design was the same as that for the two spatial discrimination tasks, except that the mouse was required to learn to run to the light or dark arm, which varied from side to side according to a Gellerman sequence. In the familiarization phase, animals were run one trial a day for 10 days. In subsequent phases, the distribution of trials was the same as for the other discrimination tasks. Almost all mice had established a side preference at the end of the free-choice phase. For these animals, the visual cue for original learning was assigned according to a statistically-determined preference during free choice. If there was no preference,

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the light or dark condition was assigned at random. For the reversal, the correct brightness cue was opposite to the one assigned for original learning. Direction of choice (both side and cue condition) was recorded for all trials.

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APPENDIX B: DATA TABLES

The decimal points have been omitted from all tables showing correlation and factor matrices. A key to the abbreviations used in the tables can be found in Table 1 in the body of the report.

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Table B1: Strain means on 79 behavioral measures

	Measure	Strain						
		C57BR/cd	C57BL/6	DBA/2	CE	CBA/Ca	LP	BALB/c
5OF	A1	244	212	209	209	132	139	140
	A5	239	194	257	256	149	170	70
	A1-5	5	18	-48	-48	-17	-31	70
	D	3.40	1.60	4.33	2.87	9.13	7.00	11.73
PJRL	1	.09	.11	.21	.15	.29	.07	.18
	5-1M	.30	.41	1.25	.52	1.13	.77	1.[illegible]
	5-1D	.28	.83	.83	.42	.57	.54	.50
	RM	.42	.38	.55	.33	1.90	.40	1.26
	RD	.11	.36	1.36	1.17	.70	1.05	.71
	5-RM	-.11	-.12	.94	.55	-.50	.53	.25
	5-RD	.40	-.04	-.37	-.54	.35	-.31	-.16
	E	.36	.65	.27	.32	.19	.64	.44
	R-E	-.02	-.07	.24	.05	-.20	.64	1.25
SMM	TCO	22	23	30	38	18	18	26
	TCR	20	28	30	29	18	26	26
	TCR-O	-2	5	6	-2	0	8	-2
	PEO	6.80	7.60	5.10	7.70	4.30	6.60	6.00
	PER	6.40	8.30	6.12	7.88	5.20	7.80	7.12
	PER-O	-.40	.70	1.00	.76	.90	1.20	1.12
	A	3.20	8.00	6.90	6.40	4.10	4.25	6.80
	TCF	12	28	24	32	14	13	17
2OF	A1	172	98	114	85	51	59	31
	A5	148	88	139	64	71	52	13
	A1-5	24	10	-25	21	-20	7	18
	L1	.9	2.2	6.2	4.1	9.4	9.5	8.5
	L5	.5	.5	1.0	2.5	1.7	14.4	43.8
	L1-5	.4	1.7	5.2	1.6	7.7	-4.9	-35.3
SDL		3.89	3.62	8.21	9.18	11.37	2.43	4.08
SBA	1	22	18	18	29	14	28	14
	4	14	16	27	31	17	14	27
	1-4	8	2	-9	-2	-3	14	-13
	$\ddot{X}$	18	16	24	29	16	20	21
E	PE	93	78	86	92	67	33	14
	L	45	145	74	85	178	201	10
	A	24	5	26	14	6	25	4
	PR	71	100	25	82	80	80	100
AJB	PF	5	10	2	2	7	43	0
	L1	.41	.33	.09	.34	.20	.33	.35
	L25M	.08	.04	.34	.03	.03	.54	.05
	L25D	.02	.02	.11	.02	.02	.06	.04
	L1-25M	.30	.30	-.15	.30	.17	-.17	.29
	L1-25D	.40	.31	-.02	.32	.18	.23	.32

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FOP	L1	.32	.58	.79	.64	4.22	.39	1.99
	L5	.23	.08	.12	.08	.18	.07	3.79
	L1-5	.09	.50	.67	.56	4.04	.32	-1.80
	A1	39.00	33.60	37.93	24.42	3.67	28.30	7.05
	A5	53.98	41.64	44.23	44.41	38.52	29.23	20.08
	A5-1	14.98	8.04	6.30	19.99	34.85	.93	13.03
SB	LE	.0271	.0370	.0328	.0364	.0768	.0368	.0663
	AV1	2.65	1.78	2.62	.15	.68	.88	1.40
	AV4-1	6.80	7.62	6.13	2.15	2.30	5.17	4.68
	AV6-4	.30	.08	.03	.70	1.34	1.83	1.03
	ITC1	24	6	19	10	7	8	22
	ITC3-1	17	29	29	28	6	18	50
	AV/C	.21	.36	.22	.03	.14	.21	.06
	ETC	8.50	4.71	2.83	3.00	10.50	2.67	1.20
SJL	1	2.15	2.64	2.89	1.50	1.95	3.00	2.15
	5	1.71	1.72	1.13	1.94	2.46	3.00	2.50
	1-5	.44	.92	1.76	-.44	-.51	.00	-.35
	$\bar{X}$	1.63	2.26	2.19	1.28	2.04	2.92	2.52
AA	TC	3.17	3.17	6.67	3.60	10.83	3.50	7.83
	L	2.94	2.96	2.29	4.55	11.67	3.65	6.51
AR	PF	15	12	2	0	39	10	22
	L57M	.16	.10	.04	.08	.08	.20	.22
	L57D	.03	.05	.04	.05	.08	.07	.05
	L1-57M	.39	.11	.02	-.03	.37	.08	-.01
	L1-57D	.67	.40	.19	-.05	.48	.24	.55
STM	TCO	15	16	18	13	14	19	30
	PEO	3.57	4.83	4.07	2.50	3.15	7.00	8.15
	A	1.78	1.25	2.20	.75	1.46	1.44	1.31
VTM	TCO	34	29	29	30	34	40	48
	TCR	60	79	39	49	49	61	66
	TCR-O	26	50	10	19	15	21	18
	PEO	7.00	7.67	8.90	7.90	8.00	9.00	8.89
	PER	6.90	7.78	6.60	5.90	7.00	8.44	8.11
	PEO-R	.10	-.11	2.30	2.00	1.00	.56	.78
	FO	14	24	27	24	28	38	47
	FR	9	29	13	4	11	28	24
	FO-R	5	-5	14	20	17	10	23

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Table 12 - Intercorrelation matrix for behavioral parameters, df = 542, (.05) = .754, p (.01) = .874

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Table B3: Unrotated principal axis factor matrix and eigen values

Measure		Factor loadings I	II	III	IV	V	VI
5OF	A1	-92	11	11	-27	25	00
	A5	-94	-11	-26	-01	-13	-13
	A1-5	54	29	54	-26	47	21
	D	95	-15	-05	04	18	-21
POBL	1	36	-79	-36	-02	21	26
	5-1M	62	-26	-63	20	33	04
	5-1D	-06	14	-44	44	14	76
	RM	70	-67	08	08	18	12
	RD	10	02	-95	02	-28	-09
	5-RM	-17	48	-82	-08	-00	-24
	5-RD	02	-49	75	26	35	-06
	E	05	85	32	24	-26	22
	R-E	69	59	-20	-16	23	-23
SWM	TCO	-33	06	-55	-76	-07	06
	TCR	-21	62	-64	-22	-09	31
	TCR-O	-13	42	-34	78	-16	21
	PEO	-42	62	31	-43	-39	08
	PER	-13	80	10	-26	-46	25
	PER-O	62	16	-62	18	-28	31
	A	-01	38	-40	-32	11	76
	TCF	-41	13	-41	-49	-26	58
2OF	A1	-88	00	23	02	33	-24
	A5	-84	-21	00	27	40	-13
	A1-5	-06	50	55	-60	-18	-24
	L1	82	-14	-39	34	-18	-12
	L5	82	42	-01	-28	24	-11
	L1-5	-71	-49	-08	39	-30	11
SDL		-03	-87	-42	-16	-13	13
SBA	1	-42	34	-11	-11	-68	-46
	4	08	-02	-70	-70	07	08
	1-4	-34	24	47	47	-50	-36
	X	-18	12	-70	-58	-24	-26
E	PE	-91	-40	-02	-11	-01	09
	L	04	-14	06	70	-67	20
	A	-52	20	-32	37	05	-67
	PR	45	22	66	-32	-35	28
AJB	PF	14	42	08	66	-54	-27
	L1	02	42	74	-41	-23	-25
	L25M	00	44	-43	67	-16	-39
	L25D	-05	24	-80	41	35	-13
	L1-25M	-02	-16	62	-72	06	26
	L1-25D	01	23	80	-50	-19	-14

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POF	L1	61	-76	05	08	05	19
	L5	74	26	04	-44	44	-01
	L1-5	-09	-83	01	42	-32	17
	A1	-86	43	-05	20	13	-11
	A5	-92	-35	14	-02	06	-08
	A5-1	19	-91	21	-27	-10	06
SB	LE	83	-51	07	-04	04	22
	AV1	-43	20	07	26	84	-04
	AV4-1	-40	59	27	35	51	18
	AV6-4	70	-04	06	25	-53	-38
	ITC1	-04	13	-02	-31	80	-50
	ITC3-1	30	59	-24	-56	37	22
	AV/C	-44	28	28	66	16	43
	ETC	-20	-77	54	27	04	-05
SJL	1	-05	53	-20	79	21	08
	5	75	11	27	17	-50	-27
	1-5	-59	26	-33	38	51	25
	X	58	50	-07	63	07	08
AA	TC	62	-67	-22	11	28	13
	T	64	-73	15	-00	-15	09
AR	PF	60	-57	48	22	14	09
	L57M	56	55	45	-04	04	-42
	L57D	60	-33	-02	41	-58	14
	L1-57M	-15	-59	66	36	16	-21
	L1-57D	25	-10	72	18	61	-08
STM	TCO	72	49	-10	-15	46	-04
	PEO	69	68	04	15	19	-05
	A	-21	-08	-23	59	71	-22
VTM	TCO	85	31	17	-09	16	-35
	TCR	15	56	71	-02	-04	39
	TCR-O	-30	40	62	03	-12	58
	PEO	58	33	-70	25	-00	-04
	PER	58	58	33	46	04	08
	PEO-R	-09	-30	-91	-25	-04	-11
	FO	89	36	-28	01	-01	02
	FR	41	69	19	43	01	37
	FO-R	57	-31	-51	-44	-02	-36
	λ	21.79	16.59	14.92	11.33	8.42	5.94
	Cumulative proportion of total variance	.28	.48	.67	.82	.92	1.00

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Table B4: Correlations between enzymes and behavioral measures

Behavior		Enzyme				
		GAD	ChAc	AChE	MAO	COMT
5OF	A1	-59	-48	-08	33	12
	A5	-32	-66	39	36	-36
	A1-5	-11	56	-72	-23	71
	D	72	66	04	-34	01
PJBL	1	38	05	39	28	-07
	5-1N	80	62	60	-36	-20
	5-1D	-12	25	30	-22	03
	PM	38	27	00	24	00
	RD	62	07	82	-49	-35
	5-RD	-27	-04	-42	72	-09
	E	-37	24	-49	-47	25
	R-E	59	81	-03	-88	27
SWM	TCO	-00	-35	25	-22	35
	TCR-O	05	27	39	-34	-46
	PEO	-63	-40	-54	-15	46
	PER	-44	-11	-43	-49	47
	PER-O	51	43	38	-64	-02
	A	-24	14	-04	-46	65
	TCF	-41	-45	05	-11	46
2OF	A1	-45	-39	-00	46	-19
	A1-5	-38	-17	-72	-14	54
	L1	78	52	40	-40	-33
	L5	50	75	-23	-72	44
	L1-5	-36	-70	35	69	-56
SDL		20	-44	49	48	-21
SBA	1	-08	-50	12	-12	-29
	4	34	-01	37	-40	36
	1-4	-32	-32	-21	23	-47
E	PE	-52	-78	16	68	-16
	L	-13	-24	10	22	-50
	A	29	-02	59	-09	-74
	PR	-40	-04	-88	-04	65
AJB	PF	13	14	06	-27	-52
	L1	-42	-16	-82	-01	44
	L25M	49	38	58	-50	-70
	L25D	60	52	82	-53	-46
	L1-25M	-58	-36	-79	38	78
	L1-25D	-51	-27	-88	16	54
FOF	L1	30	10	04	35	-04
	L5	39	70	-29	-56	59
	L1-5	-07	-48	27	73	-51
	A1	-39	-21	14	02	-23
	A5	-52	-71	09	72	-25
	A5-1	-02	-44	-09	70	04

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SB	LE	36	29	-11	07	18
	AV1	-12	35	08	04	-07
	AV4-1	-41	33	-24	-14	10
	AV6-4	52	20	03	-21	-33
	ITC1	33	43	07	-18	10
	ITC3-1	13	52	-18	-75	73
	AV/C	-56	05	-16	18	-12
	ETC	-30	-43	-16	94	-32
SJL	1	13	56	29	-42	-38
	5	34	25	-25	-25	-10
	1-5	-17	18	37	-00	-18
	X	37	80	05	-61	-16
AA	TC	53	33	29	14	-10
	L	27	-02	-06	36	-02
AR	PF	11	20	-30	41	-00
	L57M	22	54	-49	-47	20
	L57D	26	01	08	06	-29
	L1-57M	-24	-24	-24	83	-35
	L1-57D	-11	40	-52	28	15
STM	TCO	49	89	-13	-77	41
	PEO	37	86	-21	-80	23
	A	32	45	52	04	-54
VTM	TCO	54	72	-25	-56	20
	TCR	-60	17	-88	-14	60
	TCR-O	-90	-21	-76	16	50
	PEO	76	69	54	-81	-19
	PER	10	70	-37	-50	09
	PEO-R	54	-12	82	-19	-25
	FO	62	75	04	-79	19
	FR	-09	62	-35	-55	22
	FO-R	78	19	41	-30	-01

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Table B5: Whole brain amino acid levels in μ mole/g br wt.

	C57BR	C57BL	DBA	CE	CBA	IP	BALB
Cysteic acid	0.3362	0.3658	0.7406	0.1169	0.2030	0.4719	0.2276
Glycoxyl phosphoryl ethanolamine (GPE)	1.6787	1.5029	1.0538	1.4964	1.2219	1.3030	1.8121
Phospo ethanolamine (OPE)	1.3642	1.2808	1.4880	1.4241	1.1365	1.3333	1.3973
Taurine	7.5000	7.6450	6.9800	7.1450	6.9550	7.4467	6.9950
Aspartic acid	3.0400	2.9300	2.9267	3.0800	2.8600	3.0600	3.4900
Serine	0.4945	0.5110	0.4867	0.6185	0.5691	0.6773	0.5395
Threonine	0.2178	0.1740	0.2300	0.2609	0.2040	0.2427	0.2881
Glutamic acid	7.9850	7.4500	8.2733	8.2350	7.3900	6.8933	8.7950
Glutamine	7.9350	6.9750	5.8600	6.0300	5.0950	5.0000	7.4450
Half-cysteine	0.0147	0.0055	0.0027	0.0444	0.0198	0.0044	0.0219
Glycine	0.9735	1.0711	0.9833	0.8260	0.6750	0.9780	0.9095
Alanine	0.3790	0.3445	0.3577	0.3500	0.3580	0.3507	0.4216
Cystine	0.0944	0.0870	0.0309	0.0729	0.0835	0.0997	0.0726
Valine	0.0914	0.0809	0.0828	0.1050	0.0822	0.0961	0.0956
Methionine	0.0123	0.0136	0.0263	0.0219	0.0177	0.0178	0.0164
Isoleucine	0.0221	0.0145	0.0171	0.0184	0.0163	0.0179	0.0216
Leucine	0.0614	0.0573	0.0768	0.0566	0.0507	0.0639	0.0559
γ-amino butyric acid (GABA)	1.8183	1.8275	1.7057	1.8465	1.7125	1.8333	1.8600
Tyrosine	0.0184	0.0241	0.0517	0.0465	0.0234	0.0170	0.0238
Phenylalanine	0.0264	0.0256	0.0249	0.0264	0.0226	0.0257	0.0287

Histidine	0.1397	0.1165	0.0944	0.0927	0.0941	0.1390	0.1230
Ornithine	0.0511	0.0664	0.0479	0.0562	0.0518	0.0696	0.0509
Lysine	0.1750	0.1111	0.1012	0.0981	0.0749	0.1390	0.0902
Ethanolamine	0.0610	0.0140	0.0349	0.0885	0.0753	0.1440	0.0250
Arginine	0.0538	0.0483	0.0600	0.0512	0.0534	0.0539	0.0424
Carnosine	0.0961	0.0763	0.0487	0.0528	0.0607	0.0630	0.0760

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ILLUSTRATIONS

Fig. A1. The water maze used for spatial discrimination learning and reversal

Fig. A2. The runway T maze used for shock escape and avoidance as well as discrimination learning

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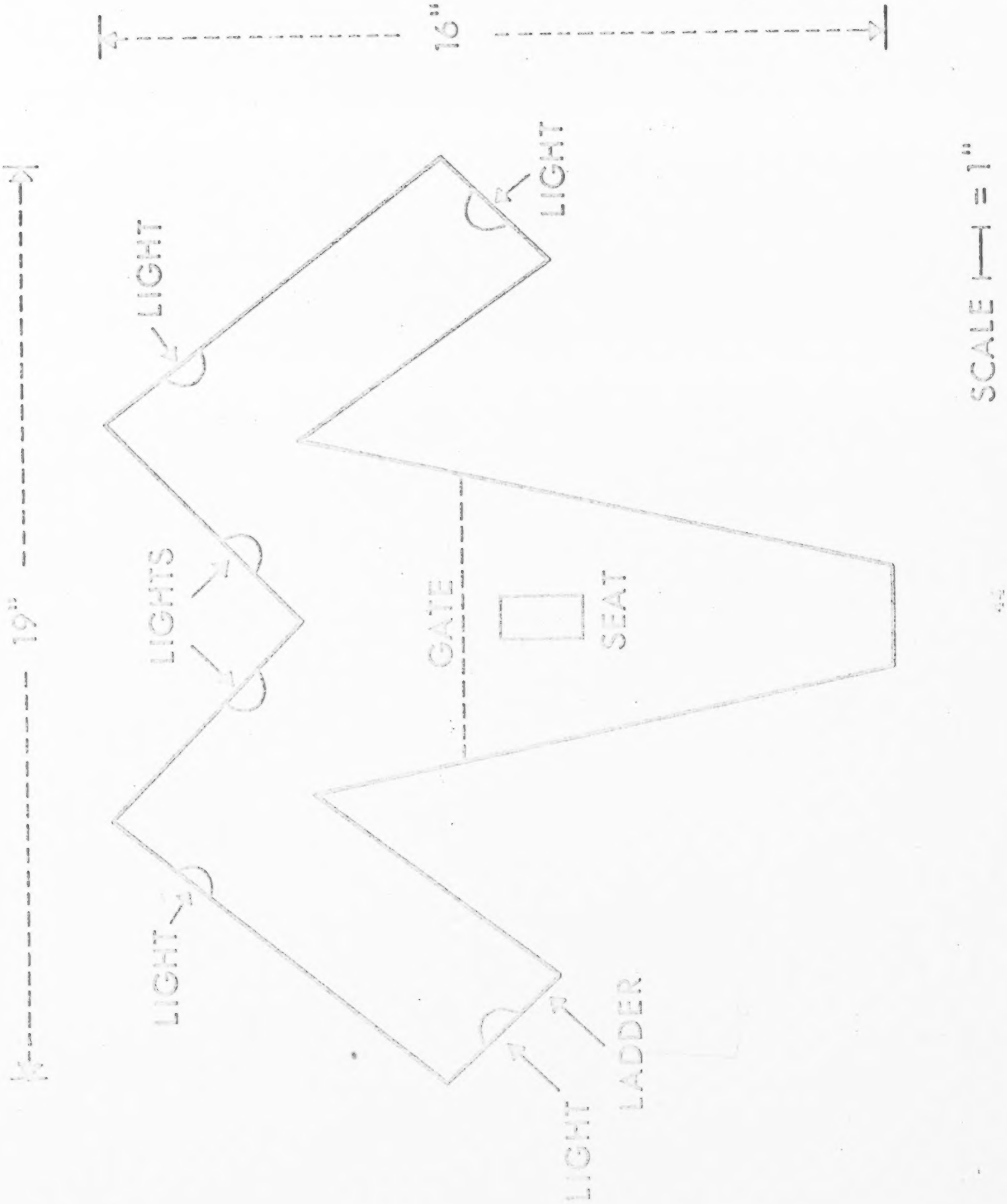

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